Effect of Metformin Versus Insulin on Maternal Weight Gain in Women with Gestational Diabetes Mellitus : A Randomized Controlled Clinical Trial

Original Article

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ABSTRACT

Aim: The aim of the study was to compare maternal weight gain in gestational diabetes mellitus (GDM) treated with metformin or insulin.

Materials and Methods: The study included 124 women with GDM, 62 of them treated with metformin, and 62 with insulin, from the outpatient clinic of Ain Shams University Maternity Hospital.

Results: The groups were comparable in age, BMI, gestational age at time of recruitment and positive family history of diabetes. Rate of maternal weight gain per week was statistically significantly lower in the metformin group compared to the insulin group. Average rate of maternal weight gain per week was 562.7 ± 111.7 gm/week in insulin group and 453.2 ± 99.58 gm/week in metformin group.

Conclusion: Metformin in women with GDM can cause less rate of maternal weight gain rather than insulin in women with GDM. While has no impact on other pregnancy maternal or neonatal outcome.

Key Words: GDM, metformin, weight

Received: 03 January 2021, **Accepted:** 30 March 2021

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ISSN: 2090-7265, August 2021, Vol.11, No. 3

INTRODUCTION

Finding an appropriate treatment for gestation DM is of most interest for obstetrician.[1] Putting in consideration that its incidence during pregnancy may reach to 16.9%[2] and adequate control of blood glucose level lead to good maternal as well as fetal outcome[1]. Inappropriate control of blood glucose level in those with gestational DM increase incidence of pregnancy complications both on maternal and fetal level, such as preeclampsia, preterm birth, caesarean section rate, birth injury, neonatal hypoglycaemia, hyperbilirubinemia, and NICU admission[3].

Pregnancy per se is associated with insulin resistance specially at the second half of it due to placental diabetogenic hormones[4]. This increasing insulin demands due to increasing its resistance through continuing and increased placental hormonal level lead to difficulty in maintaining adequate glucose level[5].

In addition to life style modification such as dietary control and maintaining physical activity, the need for pharmaceutical agent to control blood glucose is mandatory in many pregnancies with GDM, finding drug to adequately control blood glucose level is challenging[6]. Insulin is the traditional safe hypoglycaemic agent used during pregnancy, but its main disadvantage is the need for multiple injections per day and frequent daily self-monitoring. So continuous search for another pharmaceutical agent is continuing[7]. Metformin, oral, widely available, hypoglycaemic agent which is used in type 2 diabetic patients. Recent clinical trials are trying to prove its safety as well as efficacy during pregnancy[8]. It is use is controversial as a first line therapy between different guidelines[6]. Metformin, a biguanide, that act through decrease liver gluconeogenesis and enhance glucose uptake by human cells at different levels, so decrease glucose level[9]. It worth mentioning that it has other mechanisms that are not fully understood, such as inhibition of mitochondrial respiration[10]. Although Metformin is well known to crosses the placenta, the embryo has few mitochondria during early gestation, and low levels of organic cation transporters that transport metformin into cells, and this leads to new understand of metformin safety in pregnancy[11].

 DOI:10.21608/ebwhj.2021.51653.1117

Metformin has been studied as well in PCO pregnant women to decrease risk of miscarriage and preterm birth[12]. However, it has though many possible disadvantages such as failure to control of blood sugar alone, and gasteronistinal side effects such as loose stool[13]. Metformin shouldn't be used in those with impaired kidney or liver functions due to rare risk of lactic acidosis associated with metformin, and this risk increase with these two conditions[14].

The effect of metformin, in comparison to insulin, on weight gain in women with GDM is, however, poorly studied.

AIM OF THE WORK

This study aims to explore the effect of either drugs in weight gain during pregnancy.

PATIENTS AND METHODS

This study included 124 pregnant women with GDM visiting the outpatient clinic of Ain-Shams University Maternity Hospital in the period between January 2018 and June 2019. Included women were singleton, with BMI (18-30 Kg/m2), diagnosed as GDM at 24-28 weeks gestation and failed to achieve adequate glycemic control by diet modification only. The diagnosis for GDM was made with 100 grams oral glucose tolerance test, according to the International Association for Diabetes and Pregnancy Study Group (IADPSG)[7]. Women with one reading ≥200 mg/dl or HbA1c ≥ 7.5% were excluded. Women with GDM were referred to nutritionist to individualise diabetic diet based on pre-pregnancy weight (30 kcal/kg/day) while (25 kcal/kg/day) for overweight and obese women. In addition, the calories were divided to comprise 55% carbohydrates, 15% proteins, and 30% lipids. A 30-minutes of walking, 3 times a week, was recommended. Unsatisfactory glycemic control was defined among patients who present more than 30% of capillary glycemia results above the reference values one week after commencing diet therapy combined with physical activity. Enrolled women were randomized using a computer-generated randomization table, to either metformin treatment (62 women), or insulin treatment (62 women). The studied primary outcome were rate of maternal weight gain during pregnancy.

All women were asked to monitor glucose level daily (fasting, and one-hour postprandial measurements) twice a week until delivery, using a home glucometer. The desirable target glucose levels were: fasting glycaemia between 70 to 90 gm/dl and one-hour postprandial blood glucose concentration < 140 gm/dl[7].

Metformin was prescribed at a dose of 500 mg three times a day to a maximum of 2000 mg/day based on the glycemic control monitored as mentioned above. Insulin therapy in the regime of multiple injections of short (regular insulin) and intermediate acting (NPH) insulin was prescribed, with a starting dose 0.7-2.0 unit /kg/day in divided doses. The insulin group received human NPH insulin. The starting dose 30 units (20 units of intermediate acting insulin and 10 units of rapid acting insulin) in the morning prior to breakfast, dose adjustments are based on glucose levels at particular time of the day. If post dinner glucose level remain elevated additional injection of rapid acting insulin was given just prior to dinner. If fasting glucose was elevated, intermediate acting insulin could be given along with the dinner dose of rapid acting insulin[7].

At the first visit all patients the age, weight before pregnancy, smoking habits and familial history of diabetes were documented. Body mass index before pregnancy was calculated retrospectively. Gestational age in weeks were calculated. Weight before delivery was measured again in all patients wearing clothes without shoes in the morning. Height was measured to the nearest 1 cm with a stadiometer. At each antenatal visit, maternal weight was documented and monitoring of blood glucose level was reviewed to modify the drug dose if needed. At 37 week of gestation maternal weight was measured and weight gain were calculated, and HBA1C was done. Mode of delivery was documented as spontaneous, assisted or caesarean section. The neonate were examined in details documenting gestational age of newborns, birth weight, any birth injuries. Apgar score was measured at 1 and 5 mintue(s) after delivery .Neonatal serum glycaemia was measured after delivery and values lower than 40 gm/dl were considered as hypoglycemia. Neonatal ICU admission if need was documented as well as the cause of admission.

STATISTICAL ANALYSIS:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (SPSS) version 24: Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. Analysis of qualitative data were done by using chi-square or Fisher exact tests, whereas analysis of quantitative data was done by using independent t-test or Mann-Whitney test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p-value* was considered significant as $P > 0.05$: Non significant, $P < 0.05$: Significant, $P < 0.01$: Highly significant.

RESULTS

A total of 124 women were included in the study. The process of recruitment and handling the study population during the course of the study is shown in the flow diagram according to the CONSORT (CONsoildated Standards of Reporting Trials) 2010 guidelines. 8 women in the

insulin group and 11 women in the metformin group were excluded throughout the course of the study due to non-compliance, failed glycemic control using metformin and shift to insulin or loss during follow up (Figure 1).

Basic demographic and clinical characteristics of women of both groups is shown in Table 1. Rate of maternal weight gain per week was statistically significantly lower in the metformin group compared to the insulin group. Average rate of maternal weight gain per week was 562.7 ± 111.7 gm/week in the insulin group and 453.2 ± 99.58 gm/week in the metformin group (Table 2). Fasting glucose levels were statistically significantly lower in the metformin group compared to the insulin group (90.49 ± 4.06 vs 93.72 ± 9.05 mg/dL, *p value 0.01*), albeit with minor clinical relevance. No statistically significant differences in postprandial glucose levels or glycosylated hemoglobin were found between the two groups.

Incidence of cesarean section was statistically significantly higher in the insulin group compared to the metformin group. However, no statistically significant differences were found between both groups regarding gestational age at termination or incidence of amniotic fluid abnormalities, maternal hypoglycemia, preeclampsia, preterm labor, fetal demise and maternal ICU admission (Table 3). No statistically significant differences were found between women of both groups regarding birth weight, 1-min and 5-min APGAR scores and incidence of NICU admission, congenital anomalies, macrosomia, birth trauma, respiratory distress and neonatal hypoglycaemia.

Table 1: Comparison between study groups regarding basic demographic and clinical characteristics

	Insulin Group	Metformin Group	*P*
Age (Yrs)			
Range	19.0 – 35.0	19.0 – 35.0	0.03
Mean±SD	30.41 ± 4.46	28.53 ± 4.42	
BMI (Kg/m2)			
Range	25.0 – 36.0	25.0 – 35.0	0.11
Median (IQR)	31.0 (28.0 – 33.0)	32.0 (29.0 – 35.0)	
Parity			
Range	0 – 6	0 - 6	0.06
Median (IQR)	2 (1 – 3)	1 (0 – 2)	
Family history of DM (%)	10 (18.52%)	4 (7.84%)	0.15
Gestational age at enrollment (wks)			
Range	28 – 34	28 - 34	0.55
Median (IQR)	32 (30 – 34)	33 (31 – 34)	

Table 2: Comparison between maternal weight gain in the two study groups.

	Insulin Group	Metformin Group	*P*
Rate of maternal weight gain (gm/wk)			
Range	400.0 – 800.0	250.0 – 660.0	
Mean±SD	562.7 ± 111.7	453.2 ± 99.58	<0.001
95%CI	531.3 – 594.2	426.1 – 480.4	

Table 3: Comparison between obstetric outcomes in the two study groups

	Insulin Group	Metformin Group	*P*
Amniotic fluid volume			
Normal	48 (88.8%)	48 (94.1%)	
Polyhydramnios	5 (9.25%)	3 (5.88%)	0.49
Oligohydramnios	1 (1.85%)	0 (0%)	
GA at termination			
Range	32.0 – 39.0	34.0 – 39.0	0.09
Median (IQR)	37.0 (37.0 – 38.0)	38.0 (37.0 – 38.0)	
Mode of delivery			
Vaginal delivery	18 (33.3%)	28 (54.9%)	0.03
Cesarean section	36 (66.6%)	23 (45.1%)	
Maternal hypogylcemia	11 (20.3%)	5 (9.8%)	0.17
Preeclampsia	1 (1.8%)	4 (7.8%)	0.19
Preterm labor	4 (7.4%)	3 (5.8%)	0.99
Fetal demise	1 (1.8%)	0 (0%)	0.99
Maternal ICU admission			
Diabetes-related causes	1 (1.8%)	0 (0%)	0.36
Other causes	7 (12.9%)	4 (7.8%)	

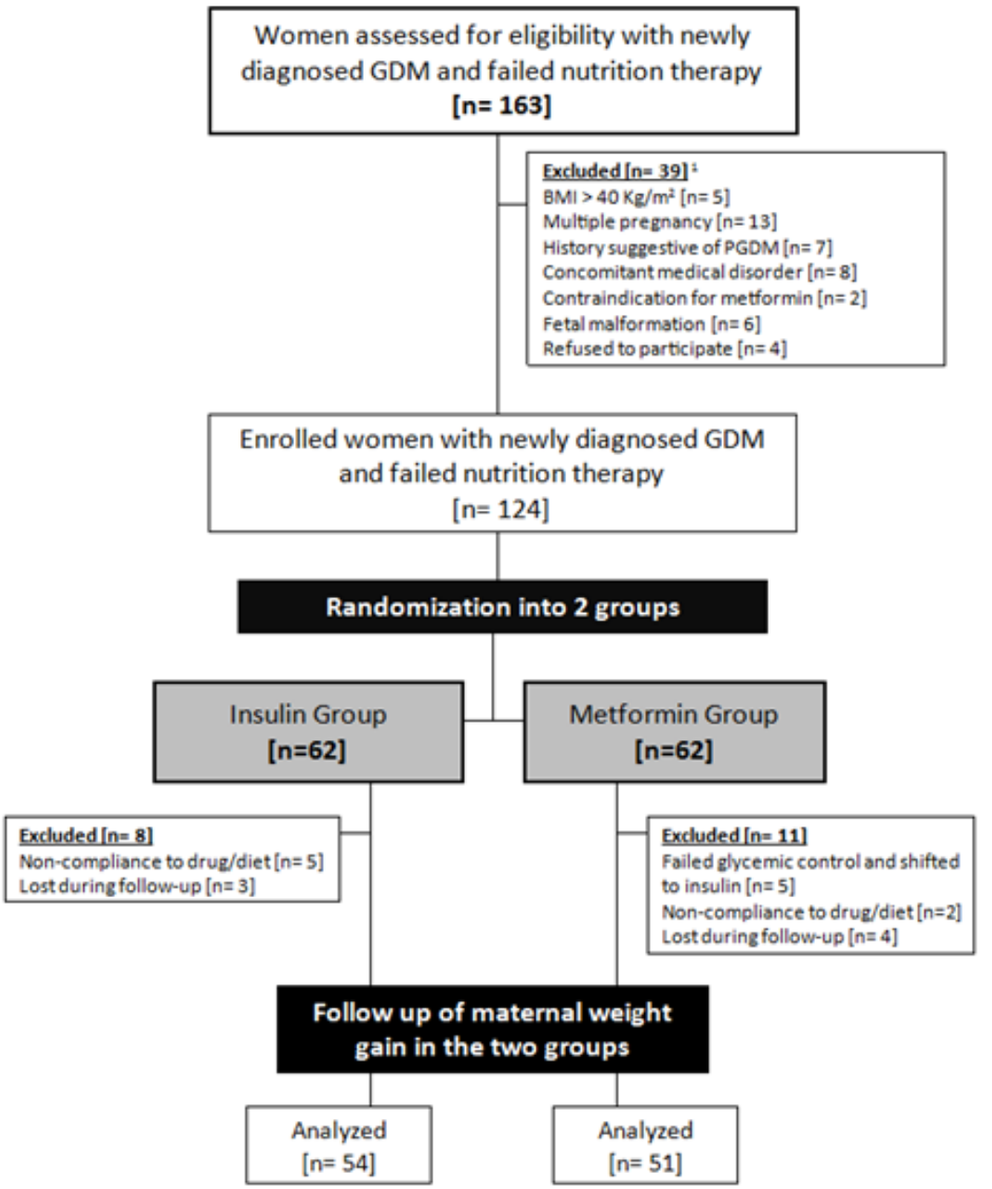

Fig. 1: CONSORT 2010 flow diagram showing the recruitment and handling of the study population during the course of the study.

[1]It should be noted the considerable overlap in the causes of exclusion in the recruited women, e.g. some women were excluded due to both multiple pregnancy and morbid obesity.

DISCUSSION

Metformin is an oral hypoglycemic that has recently been used in treatment of GDM. This study aimed to explore its effect on maternal weight gain during pregnancy, which might impact the effects of obesity on maternal and neonatal outcomes.

The results of our study showed that the rate of maternal weight gain per week was statistically significantly lower in the metformin group compared to the insulin group. In their study, Priya and Kalra[15] agreed with our findings regarding weight gain during pregnancy in those on metformin as first line therapy compared with those on insulin. Many studies showed the same significant difference in weight gain such as Ainuddin *et al.*[16] as well as Iftakhar[17]. However, it is worth mentioning that our study is unique in comparing weight gain rate per week, not only comparing the starting and the end of pregnancy weight, which might be affected by duration of follow up or timing pregnancy.

Fasting glucose levels were statistically significantly lower in the metformin group compared to the insulin group, albeit with minor clinical relevance. No statistically significant differences in postprandial glucose levels or glycosylated hemoglobin were found between the two groups. This agree with Ashley *et al.*[18], findings, declaring that although 43% required supplemental insulin to achieve glycemic control. Glucose measures did not differ between the groups, and the proportion who met fasting and postprandial glycemic target values did not differ between the groups. Women treated with metformin had significantly fewer subjective episodes of hypoglycemia compared with those using insulin[18].

Cristiane *et al.*[19] concluded that metformin was ound to have adequate glycemic control with lower mean glucose levels throughout the day. This in consensus with our study. Metformin tendency to morning hypoglycemia and so better control of fating glucose level may be due to suppression of hepatic gluconeogenesis.

In contrast to our study, Bansal *et al.* study[20] found that post prandial glucose values after 2-hour of oral glucose were slightly high in the insulin group than in the metformin group ($p < 0.003$). Also, Waheed *et al.*[21] found that there was no marked difference in efficacy of metformin and insulin in controlling diabetes in pregnant patients in the two groups. However, these disagreements may be due different insulin regimen.

Our study found no statically significant difference between insulin and metformin groups regarding pregnancy induced hypertension (1.8% vs 7.8% in insulin and metformin groups respectively). In contrast to our study, Zhao *et al.* study[22] found that metformin had statistically significant effect on pregnancy-induced hypertension [RR 0.54; 95% confidence interval (CI) 0.31; 0.91]. Also, Balani *et al.*[23] found that incidence of preeclampsia is higher in insulin group than in metformin group (*P value = 0.06*). These disagreements may be due different inclusion and exclusion criteria as we exclude many risk factors of having medical disorders as gestational hypertension.

Our study found no statistically significant differences between women of both groups regarding incidence of fetal macrosomia (22.2% in insulin group and 13.7% in metformin group, $P = 0.31$). In agreement with us, Rachel *et al.* study[24] found that there was no difference between the two groups regarding incidence of macrosomia. Also, Elahe Mesdaghinia *et al.*[25] found that no statistical difference regarding incidence of macrosomia between insulin and metformin groups. In contrast, Priya and Kalra study[15] found that women on metformin had lower risk of fetal macrosomia compared to insulin group. These disagreements may be due to the difference in the gestational ages at enrolment, therapeutic regimens used and compliance of pregnant women included in the studies.

CONCLUSION

In conclusion, treatment of GDM with metformin is associated with lower maternal weight gain, compared to insulin treatment.

CONFLICT OF INTEREST

There are no conflicts of interests.

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